REMARKS

Rejections under 35 U.S.C. §112, first paragraph

The Examiner maintains the rejection of claims 1, 6, and 7 under 35 U.S.C. §112, first paragraph for lack of written description. The Examiner asserts that the term "Fas antagonist" is not supported in the specification. The Examiner further asserts that there is no clear definition for the term in the specification. Applicants traverse this rejection and the Examiner's attention is directed to page 13, lines 1-6 of the specification, wherein a Fas antagonist is clearly defined as "a substance that blocks signal generation by Fas or blocks a generated signal from Fas-Fas ligand binding." However, in the interest of expediting the allowance of the claims, Applicants have amended claim 1 as suggested by the Examiner to recite "a substance that inhibits Fas-Fas ligand binding." As such, the rejection is overcome and withdrawal thereof is respectfully requested.

Rejections under 35 U.S.C. §102

Claims 1, 6 and 7 have been rejected under 35 U.S.C. §102 as being anticipated by U.S. Pat. No. 6,339,327. The '327 patent is asserted teach a protein, which is a Fas antagonist that binds to the intracellular domain of Fas, and the possible use of the protein to treat diseases, including multiple sclerosis. Claim 1 has been amended to define the Fas antagonist used in the present invention as "a Fas antagonist, which is a substance that

inhibits Fas-Fas ligand binding and suppresses apoptosis."

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997).

As noted by the Examiner, the protein of the '327 patent binds to the intracellular domain of Fas. The Fas antagonist of the present invention, on the other hand, inhibits Fas-Fas ligand binding. As such, the protein of the '327 patent does not fall within the present claims and the present invention is not anticipated by the reference. Withdrawal of the rejection is therefore respectfully requested.

Rejections under 35 U.S.C. §103

The Examiner has maintained several of the rejections as being obvious over the indicated references. Each rejection will be addressed in turn below. However, the following initial comments are relevant to all of the rejections under 35 U.S.C. §103.

The Examiner's position appears to be based on the following three evaluations and conclusions regarding the prior art.

1) Fas antagonists were known in the prior art. Keana et al., Hughes and Crispe, Lynch et al. and Nagata et al. are relied on in support of this evaluation.

2) The involvement of the Fas pathway in the development of MS has been suggested in the prior art. Keana et al., Holoshitz

et al. and D'Souza et al. are relied on for this evaluation.

3) From 1) and 2) the Examiner concludes that it would therefore be obvious to use a Fas antagonist to treat MS.

However, there is a key element missing from the teachings of the references, which cannot be inferred to the references to teach conclusion 3) absent some evidence. None of the references relied upon by the Examiner directly show the relationship between the Fas pathway and MS. The unpredictability of the field precludes the inference made by the Examiner that it would be obvious to treat MS using a Fas antagonist.

Attached hereto is an article by Elliott et al., *J. Clin. Invest.* 98:1602-1612 (1996), which is also cited on page 7, line 11 of the specification. Elliott et al. teach that EAE of comparable severity was observed in both wild-type and Fas deficient mice (see page 1608, right column lines 4-2 from the bottom). Thus, as indicated on page 7, lines 11-17 of the specification, this reference teaches that the Fas/Fas ligand system is not involved in MS. As discussed below, several of the references relied upon by the Examiner also teach away from using Fas antagonists. These references show the unpredictability of the field of the invention and the unobviousness of the invention. The present inventors have demonstrated for the first time that administration of a substance that inhibits Fas-Fas ligand binding is efficacious in treating MS. This finding was not suggested by, nor could be predicted from the prior art.

1) Keana et al. - The Examiner maintains the rejection of

claims 1-3 and 7 as being obvious over Keana et al. The Examiner maintains that it would be obvious to treat MS with the specific compounds of the reference. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Claim 1 has been amended as indicated above, to define the Fas antagonist used in the method of the present invention as being "a Fas antagonist, which is a substance that inhibits Fas-Fas ligand binding and suppresses apoptosis."

As stated in column 3, lines 17-34, the compounds of Keana et al. are dipeptide-based caspase inhibitors. As further described in column 1, final line, spanning column 2, line 15, "capases" is the family name for enzymes that are substrate-specific cysteine proteases that cleave inactive prointerleukin-1 to produce mature IL-1. Thus, the present invention, which is drawn a method using Fas antagonist which inhibits Fas-Fas ligand binding and suppresses apoptosis does not encompass the compounds of Keana et al.

The present invention is not achieved or suggested by the disclosure in Keana et al. As noted previously, one skilled in the art would not be able to predict from the disclosure of Keana et al. whether administration of a Fas antagonist that inhibits Fas-Fas ligand binding and suppresses apoptosis would be efficacious in treating demyelinating diseases. As such, the present invention is not obvious over Keana et al. and withdrawal of the rejection is respectfully requested.

2) *Hughes and Crispe combined with Holoshitz et al.* - The Examiner maintains the rejection of claims 1-3, 6 and 7 as being obvious over Hughes and Crispe combined with Holoshitz et al. and D'Souza et al. On page 8, first paragraph of the Office Action, the Examiner presents the position that the present claims do not require that the Fas antagonist act to inhibit apoptosis. The position of the Examiner is that D'Souza et al. teaches that Fas is involved with MS even if not through the direct result of apoptosis. The Examiner appears to take a similar position regarding Holoshitz et al. in the second paragraph of page 8 of the Office Action.

Applicants traverse this rejection and withdrawal thereof is respectfully requested. The present invention has been further defined in claim 1 to specifically require that the method comprises the administration of a Fas antagonist, which inhibits Fas-Fas ligand binding and suppresses apoptosis.

As noted previously, column 2, lines 28-35 of Holoshitz et al. teaches that the subject matter disclosed therein is drawn to the use of sphinogmyelin signal transduction inhibitors having an "apoptosis **inducing** activity" for treating RA and that sphingomyelin signal transduction inhibitors may be used to treat RA. Thus, Holoshitz et al. teach the opposite of present invention and direct one skilled in the art to seek apoptosis inducing compounds, whereas the present invention requires apoptosis inhibitory compounds.

Regarding the Examiner's evaluation of D'Souza et al.,

Applicants note that claim 1 has been amended to specifically define the Fas antagonist used in the present invention as being a substance, which inhibits Fas-Fas ligand binding and suppresses apoptosis. Thus, the disclosure in D'Souza et al. that apoptosis is not seen when OLs are stimulated with anti-Fas antibodies is relevant and teaches away from an involvement of Fas-Fas ligand in MS. One skilled in the art would conclude from D'Souza et al. that a Fas antagonist would not likely have efficacy in treating MS because of the lack of effect on OLs by anti-Fas antibodies. Thus, D'Souza et al. and Holoshitz et al. fail to compensate for the deficiencies of Hughes and Crispe and the present invention is not achieved by the combined references. Withdrawal of the rejection is respectfully requested.

3) *Lynch et al., in view of D'Souza et al.* - Claims 1-3, 5 and 6 remain rejected as being obvious over Lynch et al., in view of D'Souza et al. Applicants traverse this rejection and withdrawal there of is respectfully requested.

As discussed above, D'Souza et al. teaches away from the present invention with results that suggest that the Fas-Fas ligand pathway is not involved with MS. Lynch et al. disclose in column 16, lines 3-14, that anti-Fas antibodies are applicable to SLE, RA and idiopathic CD4+ T lymphocytopenia and HIV infection. However, Lynch et al. is silent regarding MS and does not disclose that MS is included with autoimmune demyelinating

diseases. As such, the invention is not achieved when D'Souza et al. and Lynch et al. are combined and withdrawal of the rejection is respectfully requested.

4) *Keana et al. or Hughes and Crispe combined with Holoshitz et al. and D'Souza et al. and Nagata et al.* - The Examiner maintains the rejection of claims 1, 3, 5, 6 and 7 as being obvious over Keana et al. or Hughes and Crispe combined with Holoshitz et al. and D'Souza et al. and Nagata et al. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As noted above, the compounds of Keana et al. are specific protease inhibitors that prevent the conversion of pro-interleukin 1β to interleukin 1β. There is no disclosure in Keana et al. of substances which inhibit the binding of Fas and Fas ligand. Both Holoshitz et al. and D'Souza et al. teach away from the use of a compound that inhibits apoptosis and thus teach away from the present invention. Nagata et al. fails to compensate for the deficiencies of Keana et al., Holoshitz et al. and D'Souza et al. because Nagata et al. is drawn to methods of treating RA, which as demonstrated previously, is not predictive of a method for treating autoimmune demyelinating diseases. As such, the present invention is not achieved by the references and withdrawal of the rejection is respectfully requested.

As the above amendments and remarks address and overcome the

objections and rejections to the specification and claims, withdrawal of the objections and rejections and issuance of the Notice of Allowability are respectfully requested.

Should the Examiner have any questions regarding the present application, he is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069), in the Washington DC area, at (703) 205-8000.

A marked-up version of the amended paragraphs of the specification and claims showing all changes is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments: Marked-up version

MARKED-UP VERSION

IN THE CLAIMS:

Claim 1 has been amended as follows.

1. (Twice Amended) A method for treating autoimmune demyelinating diseases which comprises administering to a patient in need thereof an effective amount of a Fas antagonist**, which is a substance that inhibits Fas-Fas ligand binding and suppresses apoptosis**.